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EXAMINER	
BERTAGNA, ANGELA MARIE	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/600,634	GUNDERSON ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-77 is/are pending in the application.

4a) Of the above claim(s) 16, 35, 52, 55-63, 73-77 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-15,17-34,36-51,53,54 and 64-72 is/are rejected.

7)☒ Claim(s) 34 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 6/20/2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10/19/05; 8/11/04; 3/3/04; 2/4/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-15, 17-34, 36-51, 53-54, and 64-72 in the reply filed on February 22, 2006 is acknowledged.

Claims 16, 35, 52, 55-63, and 73-77 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 26, 2006.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

2. Claim 34 is objected to because of the following informalities: This claim as recited depends from claim 2, but it appears to depend from claim 18. For examination, it has been treated as depending from claim 18. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites the limitation "said array" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 19 recites the limitation "said native genome" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-7, 11, 14-15, 17-20, 22-26, 30, 33-34 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (PNAS, 1992).

With regard to claim 1, Zhang et al. disclose a method of detecting typable loci of a genome, comprising the steps of:

(a) providing an amplified representative population of genome fragments comprising said typable loci, wherein said population comprises a high complexity representation (Materials & Methods section, page 5847, where individual human sperm cells were amplified by primer extension preamplification (PEP))

(b) contacting said genome fragments with a plurality of nucleic acid probes having sequences corresponding to said typable loci under conditions wherein probe-fragment hybrids are formed, wherein said probes are at most 125 nucleotides in length (Materials & Methods, page 5847, where nested PCR was used to detect type 12 loci. The inner primers of the nested PCRs correspond to the instantly claimed "nucleic acid probes having a sequence corresponding to said typable loci", as probe-fragment hybrids are formed during the annealing phase of the PCR. Also, these probes are less than 125 nucleotides in length.)

(c) detecting typable loci of said probe-fragment hybrids (see Materials & Methods, page 5847, where typable loci are detected by gel electrophoresis).

With regard to claim 2, Zhang et al. disclose method of claim 1, wherein said population of representative genome fragments comprises sequences identical to at least 5% of the genome (page 5847, column 1, where ~80% of the genome is amplified by PEP).

With regard to claim 3, Zhang et al. disclose method of claim 1, wherein said providing in step (a) comprises representationally amplifying a native genome (Materials and Methods, page 5847, where PEP is used to amplify human sperm. Note that PEP is an unbiased amplification technique, and therefore, can be considered to be a "representationally amplifying" method)

With regard to claim 4, Zhang et al. disclose method of claim 3, wherein said representationally amplifying comprises using a polymerase of low processivity (page 5847, column 2, Taq polymerase is used at 55°C).

With regard to claim 5, the Taq polymerase used by Zhang et al. inherently has a processivity rate of less than 100 bases per polymerization event (see Roche PCR applications manual, Chapter 2, where Taq polymerase is shown to have a processivity of 50 bp).

With regard to claim 6, Zhang et al. disclose the method of claim 3, wherein said representationally amplifying comprises a single step reaction yielding a high complexity representation (page 5847, where the PEP reaction comprises a single step reaction). A "single step reaction" has been interpreted to mean a "closed tube" reaction, because according to the specification, the term "a single step reaction" only appears to differentiate between the pooling of multiple, separate amplifications and performing a single amplification reaction (paragraph 153). Also, in the Examples, only single amplification reactions comprising multiple different temperature steps were conducted to produce representationally amplified samples. Therefore, the disclosure of Zhang et al. meets the instant limitation.

With regard to claim 7, Zhang et al. disclose method of claim 3, wherein at most 1×10^6 copies of said native genome are used as a template for amplification (page 5847, where single sperm cells, each containing one native genome copy were amplified using PEP).

With regard to claim 11, Zhang et al. disclose the method of claim 1, wherein said genome is a human genome (page 5847, where human sperm are subjected to PEP).

With regard to claim 14, Zhang et al. disclose the method of claim 1, wherein said probes comprise nucleic acid probes that are at least 20 nucleotides in length (page 5847, where the nested primer specific for the Y chromosome-linked pseudogene is 32 nucleotides in length).

With regard to claim 15, Zhang et al. disclose method of claim 1, further comprising producing a report identifying said typable loci that are detected (the PNAS article published in 1994 is a report identifying the typable loci that were detected).

With regard to claim 17, Zhang et al. disclose the method of claim 1, wherein step (c) comprises directly detecting said typable loci of said fragments that hybridize to said probes (see Figure 2 where the typable loci are directly detected by agarose gel electrophoresis).

With regard to claim 18, Zhang et al. disclose method of detecting typable loci of a genome, comprising the steps of:

(a) providing an amplified representative population of genome fragments comprising said typable loci (Materials & Methods section, page 5847, where individual human sperm cells were amplified by primer extension preamplification (PEP))

(b) contacting said genome fragments with a plurality of nucleic acid probes having sequences corresponding to said typable loci under conditions wherein probe-fragment hybrids are formed (Materials & Methods, page 5847, where nested PCR was used to detect type 12 loci. The inner primers of the nested PCRs correspond to the instantly claimed "nucleic acid probes having a sequence corresponding to said typable loci", as probe-fragment hybrids are formed during the annealing phase of the PCR.)

(c) directly detecting typable loci of said probe-fragment hybrids (see Materials & Methods, page 5847, where typable loci are directly detected by gel electrophoresis).

With regard to claim 19, Zhang et al. disclose the method of claim 18, wherein at most 1000 copies of said native genome are amplified (page 5848, column 2, where PEP produces an average of 62.46 copies of the native genome).

With regard to claim 20, Zhang et al. disclose the method of claim 18, wherein said population of representative genome fragments comprises sequences identical to at least 60% of the genome (page 5847, column 1, where PEP copies at least 78% of the genome).

With regard to claim 22, Zhang et al. disclose the method of claim 18, wherein said providing in step (a) comprises representationally amplifying a native genome (page 5847, where PEP is a method of representational amplification).

With regard to claim 23, Zhang et al. disclose method of claim 22, wherein said representatiorially amplifying comprises using a polymerase of low processivity (page 5847, column 2, where Taq functions as a low processivity polymerase at the disclosed reaction temperature of 55°C).

With regard to claim 24, Zhang et al. disclose the method of claim 22, wherein said low processivity is less than 100 bases per polymerization event (see Roche PCR applications manual, Chapter 2, where Taq polymerase is shown to have a processivity of 50 bp).

With regard to claim 25, Zhang et al. disclose the method of claim 22, wherein said representationally amplifying comprises a single step reaction yielding a high complexity representation (page 5847, where the PEP reaction comprises a single step reaction, because this reaction produces a high complexity representation without the requirement for subsequent reactions).

With regard to claim 26, Zhang et al. disclose the method of claim 22, wherein at most 1×10^6 copies of said native genome are used as a template for amplification (page 5847, where single sperm cells, each containing one native genome copy were amplified using PEP).

With regard to claim 30, Zhang et al. disclose the method of claim 18, wherein said genome is a human genome (page 5847, where human sperm cells are used).

With regard to claim 33, Zhang et al. disclose the method of claim 18, wherein said probes comprise nucleic acid probes are at least 20 nucleotides in length (page

5847, where the nested primer specific for the Y chromosome-linked pseudogene is 32 nucleotides in length).

With regard to claim 34, Zhang et al. disclose the method of claim 18, further comprising producing a report identifying said typable loci that are detected (the PNAS article published in 1994 is a report identifying the typable loci that were detected).

With regard to claim 36, Zhang et al. disclose the method of claim 18, wherein step (c) comprises directly detecting said typable loci of said fragments that hybridize to said probes (see Figure 2 where the typable loci are directly detected by agarose gel electrophoresis).

6. Claims 1-3, 7-12, 14-15, 17-18, 20-22, 26-31, 33-34, 36-39, 42-48, 50-51, 53-54, 64, 66, and 72 are rejected under 35 U.S.C. 102(e) as being anticipated by Wigler et al. (US Pub. No. 2004/0137473 A1). This pre-grant publication claims priority from the Divisional Application (09/561,881) filed May 1, 2000.

With regard to claim 1, Wigler et al. disclose a method of detecting typable loci of a genome, comprising the steps of:

(a) providing an amplified representative population of genome fragments comprising said typable loci, wherein said population comprises a high complexity representation (paragraph 115, page 10)

(b) contacting said genome fragments with a plurality of nucleic acid probes having sequences corresponding to said typable loci under conditions wherein probe-fragment hybrids are formed, wherein said probes are at most 125 nucleotides in length

(page 16, paragraphs 197-198, where a low complexity representation is used; paragraph 229 teaches the use of the high complexity representation; paragraph 208 teaches the use of oligonucleotide arrays, and the cited reference (Cho et al., PNAS , 1998) teaches that the probes of 25 nucleotides were immobilized on these arrays)

(c) detecting typable loci of said probe-fragment hybrids (paragraphs 197-198 teach hybridization to arrays of probes; paragraph 164 teaches detection of the loci identified by their hybridization to the complementary probe immobilized on an array).

With regard to claim 2, Wigler et al. disclose method of claim 1, wherein said population of representative genome fragments comprises sequences identical to at least 5% of the genome (paragraph 116).

With regard to claim 3, Wigler et al. disclose the method of claim 1, wherein said providing in step (a) comprises representationally amplifying a native genome (paragraphs 115-116)

With regard to claim 7, Wigler et al. disclose the method of claim 3, wherein at most 1×10^6 copies of said native genome are used as a template for amplification (paragraph 115, where 5-10 ng of DNA corresponds to approximately 6×10^3 copies of the native genome).

With regard to claim 8, Wigler et al. disclose the method of claim 1, wherein said nucleic acid probes are immobilized on a substrate (paragraphs 197-198 teach the use of arrays of probes).

With regard to claim 9, Wigler et al. disclose the method of claim 8, wherein said substrate is selected from the group consisting of a particle, bead, surface, slide, and microchip (paragraph 86).

With regard to claim 10, Wigler et al. disclose the method of claim 1, wherein at least 100 typable loci are simultaneously detected (paragraph 198, where 1000 probes are used).

With regard to claim 11, Wigler et al. disclose the method of claim 1, wherein said genome is a human genome (paragraph 49 teaches the use of genomic DNA and paragraph 52 teaches that the sample may be from a human).

With regard to claim 12, Wigler et al. disclose the method of claim 1, wherein step (b) comprises contacting said genome fragments with a multiplexed array of nucleic acid probes (paragraph 198).

With regard to claim 14, Wigler et al. disclose the method of claim 1, wherein said probes comprise nucleic acid probes that are at least 20 nucleotides in length (paragraph 208 teaches the use of oligonucleotide arrays, and the cited reference (Cho et al., PNAS, 1998) teaches that the probes of 25 nucleotides were immobilized on these arrays).

With regard to claim 15, Wigler et al. disclose method of claim 1, further comprising producing a report identifying said typable loci that are detected (paragraph 165, where a spreadsheet is generated).

With regard to claim 17, Wigler et al. disclose the method of claim 1, wherein step (c) comprises directly detecting said typable loci of said fragments that hybridize to

said probes (paragraph 198, where the loci are detected based on the fluorescence signal generated upon hybridization to the immobilized complement).

With regard to claim 18, Wigler et al. disclose method of detecting typable loci of a genome, comprising the steps of:

(a) providing an amplified representative population of genome fragments comprising said typable loci (paragraph 115, page 10)

(b) contacting said genome fragments with a plurality of nucleic acid probes having sequences corresponding to said typable loci under conditions wherein probe-fragment hybrids are formed (page 16, paragraphs 197-198, where a low complexity representation is used; paragraph 229 teaches the use of the high complexity representation; paragraph 208 teaches the use of oligonucleotide arrays)

(c) directly detecting typable loci of said probe-fragment hybrids (paragraphs 197-198 teach hybridization to arrays of probes; paragraph 164 teaches detection of the loci identified by their hybridization to the complementary probe immobilized on an array).

With regard to claim 20, Wigler et al. disclose the method of claim 18, wherein said population of representative genome fragments comprises sequences identical to at least 60% of the genome (paragraph 116).

With regard to claim 21, Wigler et al. disclose the method of claim 18, wherein said plurality of nucleic acid probes has sequences for typable loci linked to at least 5% of the expressed sequences of said genome (paragraph 204, where the cited reference (Schena et al., PNAS, 1996) teaches the use of an array designed to monitor

expression of 1000 human genes). If the number of human genes is taken to be ~30,000 (a more recent estimate than the ~100,000 genes given in Schena et al.), and 3 percent of these genes are expressed (900 expressed sequences), the 1000 probe array of Schena et al. meets the instant limitation.

With regard to claim 22, Wigler et al. disclose the method of claim 18, wherein said providing in step (a) comprises representationally amplifying a native genome (paragraphs 115-116).

With regard to claim 26, Wigler et al. disclose the method of claim 22, wherein at most 1 x 10^6 copies of said native genome are used as a template for amplification (paragraph 115, where the 5-10 ng of genomic DNA corresponds to approximately 3000 cells and 6000 copies of the genome).

With regard to claim 27, Wigler et al. disclose the method of claim 18, wherein said nucleic acid probes are immobilized on a substrate (paragraphs 197-198 teach the use of arrays of probes).

With regard to claim 28, Wigler et al. disclose the method of claim 18, wherein said substrate is selected from the group consisting of a particle, bead, surface, slide, and microchip (paragraph 84).

With regard to claim 29, Wigler et al. disclose the method of claim 18, wherein at least 100 typable loci are simultaneously detected (paragraph 198, where 1000 probes are used).

With regard to claim 30, Wigler et al. disclose the method of claim 18, wherein said genome is a human genome (paragraph 49 teaches the use of genomic DNA and paragraph 52 teaches that sample may be taken from a human).

With regard to claim 31, Wigler et al. disclose the method of claim 18, wherein step (b) comprises contacting said genome fragments with a multiplexed array of nucleic acid probes (paragraph 198).

With regard to claim 33, Wigler et al. disclose the method of claim 18, wherein said probes comprise nucleic acid probes are at least 20 nucleotides in length (paragraph 208 teaches the use of oligonucleotide arrays, and the cited reference (Cho et al., PNAS, 1998) teaches that the probes of 25 nucleotides were immobilized on these arrays).

With regard to claim 34, Wigler et al. disclose the method of claim 18, further comprising producing a report identifying said typable loci that are detected (paragraph 165, where a spreadsheet is generated).

With regard to claim 36, Wigler et al. disclose the method of claim 18, wherein step (c) comprises directly detecting said typable loci of said fragments that hybridize to said probes (paragraph 198, where the loci are detected based on the fluorescence signal generated upon hybridization to the immobilized complement).

With regard to claim 37, Wigler et al. disclose a method of detecting typable loci of a genome, comprising the steps of:

(a) providing an amplified representative population of genome fragments comprising said typable loci (paragraph 115)

(b) contacting said genome fragments with a plurality of immobilized nucleic acid probes having sequences corresponding to said typable loci under conditions wherein immobilized probe-fragment hybrids are formed (page 16, paragraphs 197-198, where a low complexity representation is used; paragraph 229 teaches the use of the high complexity representation; paragraph 208 teaches the use of oligonucleotide arrays)

(c) modifying said immobilized probe-fragment hybrids (paragraph 67, where an extension reaction is performed on immobilized probe-fragment hybrids)

(d) detecting a probe or fragment modified in step (c), thereby detecting said typable loci of said genome (paragraph 67, where the results are detected by fluorescence).

With regard to claim 38, Wigler et al. disclose the method of claim 37, wherein said plurality of nucleic acid probes has sequences for typable loci linked to at least 10% of the expressed sequences of said genome (paragraph 204, where the cited reference (Schena et al., PNAS, 1996) teaches the use of an array designed to monitor expression of 1000 human genes). If the number of human genes is taken to be ~30,000 (a more recent estimate than the ~100,000 genes given in Schena et al.), and 3 percent of these genes are expressed (900 expressed sequences), the 1000 probe array of Schena et al. meets the instant limitation.

With regard to claim 39, Wigler et al. disclose the method of claim 37, wherein said providing in step (a) comprises representationally amplifying a native genome (paragraphs 115-116).

With regard to claim 42, Wigler et al. disclose that said representationally amplifying comprises a single-step reaction yielding a high complexity representation (paragraph 115). As discussed above, the term "single step reaction" only appears to prohibit the pooling of multiple amplification reactions. Although the amplification reaction of Wigler et al. is preceded by ligation of adaptors, the "single-step" amplification reaction produces a high complexity representation.

With regard to claim 43, Wigler et al. disclose the method of claim 39, wherein at most 1×10^6 copies of said native genome are used as a template for amplification (paragraph 115, where the 5-10 ng of genomic DNA corresponds to approximately 3000 cells and 6000 copies of the genome).

With regard to claim 44, Wigler et al. disclose the method of claim 37, wherein said nucleic acid probes are immobilized on a substrate (paragraphs 197-198 teach the use of arrays of probes).

With regard to claim 45, Wigler et al. disclose the method of claim 44, wherein said substrate is selected from the group consisting of a particle, bead, surface, slide, and microchip (paragraph 84).

With regard to claim 46, Wigler et al. disclose the method of claim 37, wherein at least 100 typable loci are simultaneously detected (paragraph 198, where 1000 probes are used).

With regard to claim 47, Wigler et al. disclose the method of claim 37, wherein said genome is a human genome (paragraph 49 teaches the use of genomic DNA and paragraph 52 further specifies that the sample may be taken from a human).

With regard to claim 48, Wigler et al. disclose the method of claim 37, wherein step (b) comprises contacting said genome fragments with a multiplexed array of nucleic acid probes (paragraph 198).

With regard to claim 50, Wigler et al. disclose the method of claim 37, wherein said probes comprise nucleic acid probes are at least 20 nucleotides in length (paragraph 208 teaches the use of oligonucleotide arrays, and the cited reference (Cho et al., PNAS, 1998) teaches that the probes of 25 nucleotides were immobilized on these arrays).

With regard to claim 51, Wigler et al. disclose the method of claim 37, further comprising producing a report identifying said typable loci that are detected (paragraph 165, where a spreadsheet is generated).

With regard to claim 53, Wigler et al. disclose the method of claim 37, wherein step (c) comprises a primer extension assay (paragraph 67).

With regard to claim 54, Wigler et al. disclose the method of claim 53, wherein said primer extension assay is selected from the group consisting of allele specific primer extension (ASPE), single base extension (SBE) and pyrosequencing (paragraph 67).

With regard to claim 64, Wigler et al. disclose a method for detecting typable loci of a genome, comprising the steps of:

(a) in vitro transcribing a population of amplified genome fragments, thereby obtaining genomic RNA fragments (paragraph 91, where RNA is transcribed from a representation of DNA)

(b) hybridizing said genomic RNA fragments with a plurality of nucleic acid probes having sequences corresponding to said typable loci, thereby forming a plurality of RNA fragment-probe hybrids (paragraph 91)

(c) detecting typable loci of said RNA fragment-probe hybrids (paragraph 91)

With regard to claim 72, Wigler et al. disclose the method of claim 64, further comprising a step of isolating said genomic RNA fragments (paragraph 91).

7. Claims 1-3, 6-7, 11, 15, 17-20, 22, 25-26, 30, 33-34 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Dean et al. (PNAS; April 2002).

With regard to claim 1, Dean et al. disclose a method of detecting typable loci of a genome, comprising the steps of:

(a) providing an amplified representative population of genome fragments comprising said typable loci, wherein said population comprises a high complexity representation (page 5261: Methods section "Amplification of human genomic DNA by MDA" and also abstract)

(b) contacting said genome fragments with a plurality of nucleic acid probes having sequences corresponding to said typable loci under conditions wherein probe-fragment hybrids are formed, wherein said probes are at most 125 nucleotides in length (page 5262, where the fragments are contacted with TaqMan probes that are less than 125 nucleotides in length)

(c) detecting typable loci of said probe-fragment hybrids (page 5262 where loci are detected using TaqMan probes).

With regard to claim 2, Dean et al. disclose method of claim 1, wherein said population of representative genome fragments comprises sequences identical to at least 5% of the genome (page 5261).

With regard to claim 3, Dean et al. disclose the method of claim 1, wherein said providing in step (a) comprises representationally amplifying a native genome (page 5261, where MDA is a method of representationally amplifying).

With regard to claim 6, Dean et al. disclose the method of claim 3, wherein said representationally amplifying comprises a single step reaction yielding a high complexity representation (page 5261, where MDA is conducted in a single isothermal step).

With regard to claim 7, Dean et al. disclose the method of claim 3, wherein at most 1×10^6 copies of said native genome are used as a template for amplification (see Table 1, page 5262).

With regard to claim 11, Dean et al. disclose the method of claim 1, wherein said genome is a human genome (page 5261, abstract).

With regard to claim 15, Dean et al. disclose method of claim 1, further comprising producing a report identifying said typable loci that are detected (Figure 3 comprises a report).

With regard to claim 17, Dean et al. disclose the method of claim 1, wherein step (c) comprises directly detecting said typable loci of said fragments that hybridize to said probes (page 5262, where loci are directly detected by the TaqMan assay).

With regard to claim 18, Dean et al. disclose method of detecting typable loci of a genome, comprising the steps of:

(a) providing an amplified representative population of genome fragments comprising said typable loci (page 5261: Methods section "Amplification of human genomic DNA by MDA" and also abstract)

(b) contacting said genome fragments with a plurality of nucleic acid probes having sequences corresponding to said typable loci under conditions wherein probe-fragment hybrids are formed (page 5262, where fragments are contacted with probes in Southern blotting or with TaqMan probes)

(c) directly detecting typable loci of said probe-fragment hybrids (page 5262, where the fragments are directly detected by Southern blotting or the TaqMan assay).

With regard to claim 19, Dean et al. disclose that at most 1000 copies of the native genome are amplified (Table 1).

With regard to claim 20, Dean et al. disclose the method of claim 18, wherein said population of representative genome fragments comprises sequences identical to at least 60% of the genome (page 5261).

With regard to claim 22, Dean et al. disclose the method of claim 18, wherein said providing in step (a) comprises representationally amplifying a native genome (abstract).

With regard to claim 25, Dean et al. disclose the method of claim 22, wherein said representationally amplifying comprises a single step reaction yielding a high complexity representation (page 5261, where MDA is conducted in a single isothermal step).

With regard to claim 26, Dean et al. disclose the method of claim 22, wherein at most 1 x 10^6 copies of said native genome are used as a template for amplification (Table 1, page 5262).

With regard to claim 30, Dean et al. disclose the method of claim 18, wherein said genome is a human genome (abstract, page 5261).

With regard to claim 33, Dean et al. disclose the method of claim 18, wherein said probes comprise nucleic acid probes are at least 20 nucleotides in length (page 5262 where the probes used in Southern blotting are inherently greater than 20 nucleotides in length).

With regard to claim 34, Dean et al. disclose the method of claim 18, further comprising producing a report identifying said typable loci that are detected (Figure 3).

With regard to claim 36, Dean et al. disclose the method of claim 18, wherein step (c) comprises directly detecting said typable loci of said fragments that hybridize to said probes (page 5262, where the direct detection occurs in Southern blotting or the TaqMan assay).

8. Claims 64, 66, 71 and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Pastinen et al. (Genome Research, 2000).

With regard to claim 64, Pastinen et al. disclose a method for detecting typable loci of a genome, comprising the steps of:

(a) in vitro transcribing a population of amplified genome fragments, thereby obtaining genomic RNA fragments (page 1038, "Multiplex PCR Amplification", where

genomic DNA fragments are produced; page 1039 "Optimization of Allele-specific extension reactions" where in vitro transcription of the multiplex PCR products results in genomic RNA fragments; see also Figure 1 for a schematic)

(b) hybridizing said genomic RNA fragments with a plurality of nucleic acid probes having sequences corresponding to said typable loci, thereby forming a plurality of RNA fragment-probe hybrids (page 1039 "Optimization of allele-specific extension reactions and Figure 1)

(c) detecting typable loci of said RNA fragment-probe hybrids (Figure 1).

With regard to claim 66, Pastinen et al. disclose that step (c) comprises modifying said genomic RNA fragment-probe hybrids with reverse transcriptase (page 1039 "Optimization of allele-specific extension reactions and Figure 1).

With regard to claim 71, Pastinen et al. disclose the method of claim 66, wherein said modifying said genomic RNA fragment-probe hybrids with reverse transcriptase occurs under conditions wherein DNA-dependent DNA synthesis is inhibited (Figure 1 and page 1039 where the absence of a DNA polymerase inhibits DNA-dependent DNA synthesis).

With regard to claim 72, Pastinen et al. disclose the method of claim 64, further comprising a step of isolating said genomic RNA fragments (Figure 1 and page 1039 where hybridization of the RNA fragments to specific array-immobilized targets results in their isolation).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 13, 32 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wigler et al. (US Pub. No. 2004/0137473 A1) in view of Maldonado-Rodriguez et al. (Molecular Biotechnology, 1999).

Wigler et al. teach the method of claims 1, 31, and 48, as discussed above.

With regard to claims 13, 32 and 49, Wigler et al. do not teach contacting the array of nucleic acid probes with chaperone probes.

Maldonado-Rodriguez et al. taught that preannealing auxiliary oligonucleotides to targets prior to contacting them with immobilized probes resulted in substantial increases in hybridization specificity and sensitivity as well as signal amplification (see abstract, especially points (1) – (4)). These auxiliary oligonucleotides are the functional equivalent of the instantly claimed chaperone probes.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize chaperone probes (or analogously "auxiliary oligonucleotides") as taught by Maldonado-Rodriguez et al. in the genotyping method of Wigler et al. in order to improve hybridization specificity, sensitivity and amplify the observed signal. Maldonado-Rodriguez et al. particularly pointed out that the preannealing of these chaperone probes to target sequences prior to hybridization to array-immobilized probes resulted in improved mismatch detection, amplification of the observed signal via base-stacking interactions between the chaperone probe and target sequence, and increased sensitivity by prevention of hybridization-blocking secondary structure formation in the target (see abstract and Discussion). These improvements to array-based hybridization experiments would have been directly applicable to the ordinary practitioner of the method of Wigler et al. and would have strongly motivated this ordinary artisan to incorporate chaperone probes as taught by Maldonado-Rodriguez et al. in order to improve the hybridization-based genotyping method in the ways outlined above.

12. Claims 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wigler et al. (US Pub. No. 2004/0137473 A1) in view of Zhang et al. (PNAS, 1992) and further in view of Graves (Trends in Biotechnology, 1999).

Wigler et al. teach the method of claim 39, as discussed above.

Wigler et al. do not teach the use of a low processivity polymerase.

With regard to claims 40-41, Zhang et al. teach a method of whole genome amplification where a low processivity polymerase (Taq) is used and this polymerase has a processivity rate of less than 100 bases per polymerization event (see Roche Technical Notes, as discussed above).

Graves teaches that an optimal target length for hybridization to high-density oligonucleotide arrays is 100-200 bases in length, and that even smaller targets of 50 bases may be used to further reduce interfering steric effects resulting from the use of long targets (page 130, "Target size" section).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize a low processivity polymerase as taught by Zhang et al. in the method of Wigler et al. in order to produce shorter targets for array hybridization. Graves taught that a shorter target length was advantageous in array-based hybridization studies in order to reduce the hybridization inhibiting steric problems often encountered with long targets (page 130). The teachings of Graves would have been directly applicable to the ordinary practitioner of the method of Wigler et al. and would have motivated this ordinary artisan to seek a method of reducing the target size. One method taught by Graves is fragmentation following amplification. However, Zhang et

al. taught that the low processivity polymerase, Taq, could generate short targets without the need for a subsequent fragmentation step. Furthermore, although Wigler et al. point out the disadvantages of the primer extension preamplification method of Zhang et al. (page 2, paragraphs 15-19), substitution of a low processivity polymerase in the adaptor-based amplification step of Wigler et al. would retain the proposed advantages of the method of Wigler et al. relative to the method of Zhang et al. while reducing the size of the resulting targets, thereby improving the subsequent hybridization reaction without the need for an additional fragmentation step. Therefore, the ordinary artisan, interested in reducing steric hindrance in the array-based hybridization of Wigler et al. by using a shorter target as taught by Graves, would have been motivated to substitute a low processivity polymerase as taught by Zhang et al., thus resulting in the instantly claimed methods.

13. Claims 65 and 67-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastinen et al. (Genome Research, 2000) in view of Zhang et al. (PNAS, 1992) and further in view of Grothues et al. (Nucleic Acids Research, 1992).

Pastinen et al. teach the method of claims 64, 66, 71, and 72, as discussed above.

Pastinen et al. do not teach the use of random primers comprising a constant region in the in vitro transcription reaction, nor do Pastinen et al. teach replication of the hybridized RNA fragments using locus-specific primers comprising a second constant

region followed by an additional replication step using primers complementary to the first and second constant region.

Zhang et al. teach a method of primer extension preamplification using random primers, as discussed above.

Grothues et al. teach a method of amplification using tagged random primers.

With regard to claim 65, Zhang et al. and Grothues et al. teach amplification of genomic DNA with random primers (abstract in Zhang et al. and page 1321, column 1 in Grothues et al.)

With regard to claim 67, Zhang et al. teach amplification of PEP products using a plurality of locus-specific primers (page 5847, column 2), but do not teach that the fragments are RNA.

With regard to claim 68, Grothues et al. teach amplification using random primers containing a 3' random region and a 5' constant sequence to produce fragments labeled with a constant sequence (2nd paragraph, column 1, page 1321), but do not teach the use of these primers in an in vitro transcription reaction.

With regard to claim 69, Zhang et al. teach the use of locus-specific primers, but do not teach that these locus-specific primers contain an additional constant region.

With regard to claim 70, Grothues et al. teach further amplification using a primer complementary to the constant tagged region (page 1321, column 1, 2nd paragraph), but do not teach that the first and second constant regions are different.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize a combination of tagged random and locus-specific primers

as taught by Zhang et al. and Grothues et al. in the method of Pastinen et al. in order to improve the accuracy of the hybridization results obtained. Pastinen et al. taught hybridization of in vitro transcribed RNA fragments to an array followed by reverse transcriptase mediated allele-specific primer extension. In the method of Pastinen et al. an amplified population of genomic fragments was produced by multiplex PCR. With regard to claims 65 and 67, the ordinary practitioner of the method of Pastinen et al. would have been motivated to incorporate the teachings of Zhang et al. and perform the genomic DNA amplification using random primers in order to eliminate the need for optimization of a complicated multiplex PCR. Then, following in vitro transcription and hybridization to immobilized probes as taught by Pastinen et al., the ordinary artisan would have been motivated to perform an amplification step using the locus-specific primers of Zhang et al. in order to provide an additional measure of the accuracy of the hybridization reaction. With regard to claims 68-70, the ordinary user of the method of Pastinen et al., would have been further motivated by the teachings of Grothues et al. to incorporate constant regions into the random and locus-specific primers, thereby enabling an additional amplification reaction using primers complementary to the constant regions, thus providing another level of control over the accuracy of the hybridization results obtained. Amplification with random primers followed by locus-specific primers was well known in the art, as was the use of tagged primers. Therefore, the ordinary artisan could have readily incorporated the teachings of Zhang et al. and Grothues et al. into the method of Pastinen et al., in order to effect the improvements discussed above. Therefore, the person of ordinary skill, interested in

improving the accuracy of the hybridization data obtained in the method of Pastinen et al., would have been motivated to incorporate tagged random and locus-specific primers as taught by Zhang et al. and Grothues et al., thus resulting in the instantly claimed methods.

Double Patenting

14. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

15. Claims 1-15, 17-34, 36-51 and 53-54 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-15, 17-34, 36-51 and 53-54 of copending Application No. 10/681,800. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

16. Claims 1-15, 17-34, 36-51, 53-54 and 64-72 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-15, 17-34, 36-51, 53-54, and 64-72 of copending Application No. 11/066,096. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 37, 39-40, and 44-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 78-80, 82, 85, 90-94, 96, 104-106, 108, 110, and 115-118 of copending Application No. 10/872,141. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 78 (combined with dependent claims 85 and 98) and 104 (combined with dependent claim 110) of 10/872,141 recite a species of the generic method of claim 37, thereby anticipating the instant claim. The limitations of the dependent claims 44-45 in the instant application are recited in claims 79, 80, 82, 105-106, and 108 of Application No. 10/872,141. The limitations of claims 90, 93, 115, and 118 in 10/872,141 are recited in claims 39 and 40 of the instant application. The limitations of claims 91-92, 94, 96, 116, and 117 in 10/872,141 are specific

embodiments of step (a) of the instant claim 37, and therefore, when combined with the independent claims 78 and 104 of 10/872,141, anticipate the instant claim 37.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claims 37, 53, and 54 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 78, 85-86, 104, and 110-111 of copending Application No. 10/872,141 in view of Wigler et al. (US Pub No. 2004/0137473 A1).

Claims 78 and 104 of 10/872,141 (combined with dependent claims 85 and 110, respectively) recite a species of the generic method of claim 37, as discussed above.

With regard to claims 53 and 54, Application No. 10/872,141 recites in claims 86 and 111 that modification comprises addition of a nucleotide or nucleotide analog using a polymerase, but does not teach a primer extension assay selected from the group consisting of ASPE, SBE and pyrosequencing.

Wigler et al. teaches the method of the instant claims 37, 53 and 54 as discussed above.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to use primer extension assays selected from ASPE, SBE and pyrosequencing in the method disclosed in 10/872,141, because Wigler et al. taught the general method of claims 78 and 104 of 10/872,141, and provided a specific example of detection comprising a primer extension assay (paragraph 67). The ordinary artisan

would have been motivated to combine these methods disclosed in 10/872,141 and Wigler et al., therefore resulting in the instant claims 37, 53 and 54.

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571) 272-8291. The examiner can normally be reached on M-F 7:30-5 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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5/15/06